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Original Article

Frequency Variation of Ventricular Fibrillation May Help Predict Successful Defibrillation in a Rat Model of Cardiac Arrest

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Background: To evaluate whether the frequency variation of ventricular fibrillation (VF) helps to predict successful defibrillation in a rat model of cardiac arrest.
Methods: VF was induced in rats followed by cardiopulmonary resuscitation and then defibrillation. The electrocardiographic signals of 30 rats with first-shock success were obtained from our previous animal experiments, and 300 rats without first-shock success were selected as control. The VF waveform immediately before the first defibrillation was analyzed.
Results: Eighty-eight percentages of the frequency variations of an electrocardiogram (ECG) record falling in the range -9.5–9.5 Hz was selected with sensitivity of 0.8, specificity of 0.583, and area under curve (AUC) of 0.708. Compared with amplitude spectrum area (AMSA) (sensitivity = 0.767, specificity = 0.547, and AUC = 0.678), combining frequency variation and AMSA significantly increases the predictability with sensitivity of 0.933, specificity of 0.493, and AUC of 0.732 ($p = 0.005$).
Conclusions: The frequency variation of VF may serve a useful parameter to predict defibrillation success.

Key words: *ventricular fibrillation, waveform, frequency variation, cardiac arrest, electric shock*

Introduction

Sudden cardiac arrest is a major health problem and ventricular fibrillation (VF) accounts for 40% of initial rhythms in sudden cardiac arrest.[1] VF, generated by multiple interacting systems within the heart, is characterized as rapid and disorganized contractions of the heart with complex but a non-random electrocardiogram (ECG) pattern,[2,3] and defibrillation is the method of choice for successful resuscitation from VF. However, defibrillation is not an innocuous therapy. Repetitive unsuccessful defibrillations would significantly increase the severity of myocardial damage[4] and compromise the ultimate success of cardiopulmonary resuscitation (CPR). Defibrillation is most effective when used very early in VF cardiac arrest and the probability of successful defibrillation decreases dramatically over time.[5,6] Waveform analysis of VF has been studied for years with several proposed and developed methods based on fractal dimension (amplitude/scaling) and frequency measurements of short segment of the signal,[7,8] which aimed to help

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determining optimal duration of CPR and appropriate timing of defibrillation. The obvious characteristic of high-amplitude, low-frequency waveform in early VF and low-amplitude, higher frequency waveform in late VF initiated the VF waveform analyses.[9,10] The fractal dimension (amplitude/scaling) based measures, including scaling exponent (ScE), logarithm of the absolute correlations (LAC), and detrended fluctuation analysis (DFA), demonstrate a decrease in organization and an increase in the fractal dimension over time due to the wavefronts break into smaller patterns and the amplitudes diminish.[11-13] On the other hand, the frequency measures contain the amplitude spectrum area (AMSA), angular velocity (AV), median and dominant frequency and frequency ratio, and show a consistent decline over time during VF due to the loss of high energy phosphates in the cardiomyocyte.[14-16] However the use of amplitude measure is limited due to its dependence on recording condition, movement artifact, body habitus, electrode placement, and recording equipment. Besides, the possibility of identical values of frequency in both early and late VF also limits the use of frequency measure.[15] In the current derivation study, by using an established rat model of VF cardiac arrest, we seek to develop a new frequency-based method to identify the difference of VF waveform between successful and unsuccessful defibrillation, and improve the predictability when combing with other methods.

Methods

The study and all the protocols used in the experiment were approved by Institutional Animal Care and Use Committee of National Taiwan University (No.: 20130135).

Animal Preparation

The male Wistar rats at the age of 14 weeks old and weighing around 400 g were used and prepared as described previously.[17] Briefly, the animals were anesthetized with an intraperitoneal injection of sodium pentobarbital (50 mg/kg body weight). The tracheas were orally intubated with a PE200 catheter and the animals were mechanically ventilated with a tidal volume of 0.65 mL/100 g body weight, a frequency of 100/min, and a fraction of inspiration O_2 (FiO_2) of 1.0. The saline-filled PE-50 tubes were inserted through the right femoral artery (FA) and through the right carotid artery and advanced into the left ventricle (LV), respectively, to measure arterial and LV pressures. The rate of increase of LV pressure at 40 mmHg (dP/dt 40) was measured to present the systolic function and the maximal negative dP/dt (-dP/dt max) was used to indicate the diastolic function. Another PE-50 tube was inserted and placed in the right jugular vein for fluid administration and pressure monitoring. To monitor temperature changes, a thermodilution-tipped catheter (ADInstruments, Sydney, Australia) was inserted through the left FA and advanced into the abdominal aorta. A personal computer (PC)-based data-acquisition system (ADInstruments) was used to record hemodynamics, temperature, and needle-probe ECGs. Before the experiment, the animals were observed for 30 min to ensure hemodynamic stability. The body temperature was maintained at 37.0 ± 0.5°C.

Current-Induced Cardiac Arrest Animal Model

The animal model of current-induced cardiac arrest has been well established and described previously.[17] To induce VF, a guide-wire was advanced from the right jugular vein into the endocardium of the right ventricle. VF was induced by increasing progressively an alternating electric current at 60 Hz to a maximum of 1 mA and continued for 1.5 min to prevent spontaneous defibrillation. The animals were left untreated for 3.5 min and the mechanical ventilation was discontinued since VF cardiac arrest was induced. After 5 min of VF, mechanical ventilation was restarted and chest compression was started with a pneumatically driven mechanical chest compressor at 200 beats/min. Chest compression and ventilation were synchronized at a compression/ventilation ratio of 2:1 with equal compression–relaxation duration. The compression depth was adjusted to secure a coronary perfusion pressure (CPP) > 20 mmHg. This typically yielded an end-tidal partial pressure of CO_2 ($ETCO_2$) of 13 ± 2 mmHg. After 1 min of CPR, one 3-J monophasic electric shock was administered (Fig. 1). A sequence of 30 sec of chest compression followed by one 5-J electric shock was applied then until return of spontaneous circulation (ROSC) was achieved or a total of four shocks, which ever came first. The electric shock was considered to be successful if the animal regained organized cardiac rhythm with mean arterial pressure more than 60 mmHg after defibrillation.

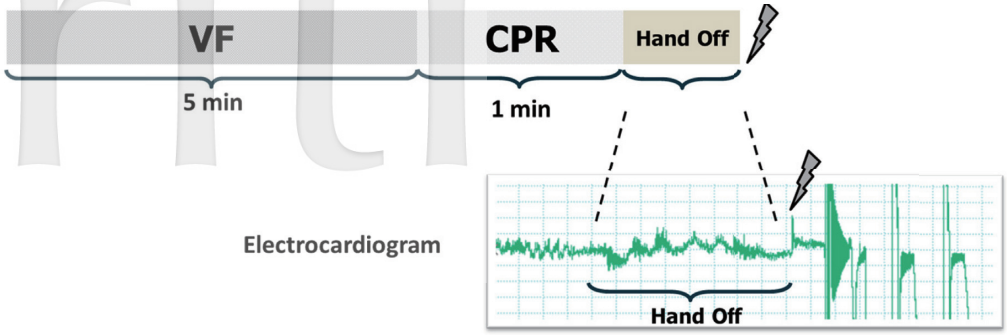

Fig. 1. Protocol of experiment.
CPR: cardiopulmonary resuscitation; VF: ventricular fibrillation.

Study Design

In the current study, we selected the electrocardiographic signals of VF waveform from our previous animal experiments, which using VF cardiac arrest model as described above, to develop a new waveform analysis model and no new experiment was performed on any animals. Thirty rats with first-shock success were selected and classified as the first-shock success group. Three hundred rats without first-shock success were selected as control and named as the first-shock failure group. The choice of the ratio was based on the fact that the number of first shock success is far less than the number of first shock failure in the animal study. The electrocardiographic signals of VF waveform immediately before the first defibrillation were obtained and analyzed (Fig. 1).

AMSA and DFA Analyses

AMSA and DFA analyses were performed as previously described.[14,18] AMSA was calculated as the sum of contributing frequencies weighted by the absolute values of the Fourier transform of the signal in the frequency range of 3–48 Hz.[14] DFAα2 was used to measure fractal-like correlation properties of the time-series of ECG signals and the size of the window on a log 1.5–2.5 scale.[18]

Measurement of Frequency Variation (FV)

For each ECG record, a 3-sec signal was extracted from this ECG record. Because the sampling rate is 1000 Hz, the 3-sec exacted signal has 3,000 samples. The exacted signal ECG was passed through a high pass filter with cutoff frequency 1 Hz in order to eliminate the baseline wander. The filtered signal was represented by $x[n]$, $n = 0, 1, \ldots, N-1$, where $N = 3{,}000$. Then the frequency domain representation of $x[n]$ could be obtained using the Fourier transform.

$$x[k] = \sum_{n=0}^{N-1} x[n]\, e^{-j\frac{2\pi}{N}nk},\ k = 0, 1, \ldots, K-1.$$

In the experiments, K is set to be 16,384. Using $x[k]$, the dominant frequency $f_{dominant}$, which corresponds to the frequency index with the strongest power of $x[k]$, can be determined. The inverse of $f_{dominant}$ could be regarded as the dominant period of a VF pulse, denoted by $T_{dominant}$. In the experiments, the value of $T_{dominant}$ was usually in the range of 60–100 (samples). That was to say, a VF pulse usually takes 60–100 samples (or 60–100 ms).

The FV of the ECG record was then calculated. The procedure of calculating the FV consisted of three steps: firstly, M pieces of signal were extracted from $x[n]$ using the following formula.

$y_m[l] = x[l + mT_{dominant}]$, $m = 0, 1, \ldots, M-1$; $l = 0, 1, \ldots, W-1$.

$y_m[l]$ denotes the mth piece of signal. In the experiments, the value of M was usually from 30 to 50. $W = \alpha T_{dominant}$, where α was set to be three. That is, each piece of signal contained around three VF pulses and there were 30–50 pieces of signals in an ECG record. Secondly, for each piece of signal $y_m[l]$, the Fourier transform was conducted again to obtain the dominant frequency of $y_m[l]$, which is denoted by f_m. Thirdly, the FV could then be calculated using the following equation:

$D_m = f_{m+1} - f_m$, $m = 0, 1, \ldots, M-1$.

There were around 30–50 FVs in an ECG record.

Combination of AMSA and FV

During experiments, the AMSA and FV methods usually made different predictions in some ECG data, implying that both the FV and AMSA methods capture important but different characteristics of ECG records for making successful predictions. Therefore, we proposed a naming AMSA + FV method to determine the threshold of the following new parameter for each ECG record:

$\beta \cdot AMSA + (1 - \beta) \cdot PFV$, $0 < \beta < 1$,

where *AMSA* was the AMSA value and *PFV* was the percentage of the FV falling in the range -9.5–9.5 Hz.

Statistical Analysis

For the continuous variables, mean ± standard deviation or median values with interquartile ranges (IQR) used to present, as appropriate. The independent t-test was used for comparisons of normally distributed continuous variables between the two groups, and the Mann–Whitney U test was used to compare the difference of variance of frequency variance between these two groups. The successfully resuscitated animals were shown as percentage and compared by using the Fisher's exact test between the two groups. Receiver operating characteristic (ROC) curves were constructed to demonstrate the predictive performance of different waveform analyses. The area under the curve (AUC) statistic and associated 95% confidence intervals (CIs) were used to estimate the overall discriminate ability of each waveform analyses. The sensitivity and specificity across the range of cut-off value of waveform parameters were also calculated. The comparison of ROC curves was performed using the method of Hanley and McNeil.[19] Data were analyzed using the SPSS 18.0 software (IBM, Armonk, NY, USA). The ROC curves were calculated and compared with MedCalc version 16.4.3 (MedCalc Software, Mariakerke, Belgium).

Results

The baseline characteristics including body weight and pre-arrest hemodynamics did not differ between these two groups. There was also no significant difference in VF-induced current, CPP and $ETCO_2$ immediately before the first electric shock (Table 1).

The proportion of studied animals was higher in the in the first-shock success group than in the first-shock failure group when the FV was less than 2 Hz. Whereas, when the FV was more than 2 Hz, the ratio in the first-shock failure group was higher than in the first-shock success group (Fig. 2A). The Fig. 2B demonstrated the distribution of variance of FV and showed that most animals in the first-shock success group had variance of FV less than 40. However, the variance of FV in the first-shock failure group mostly located from 20 to 60. The median value of variance of FV in animals with first-shock success was significantly less than those without first-shock success (21.51 [IQR = 11.99–36.49] vs. 39.42 [IQR = 23.28–52.88], $p < 0.001$) (Supplement Table 1).

From the experimental results, we observed that when 88% of the FVs of an ECG record fell in the range between -9.5 and +9.5 Hz, the successful rate of deliberation was high. On the other hand, when most

Table 1. Baseline characteristics before defibrillation between groups

Parameter	First-shock success group (n = 30)	First-shock failure group (n = 300)	*p*
Body weight (g)	411.67 ± 56.59	406.47 ± 49.85	0.591
Heart rate (/min) before arrest	429.70 ± 35.05	424.91 ± 33.44	0.501
Mean arterial pressure (mmHg) before arrest	101.80 ± 7.37	101.54 ± 7.99	0.877
dp/dt 40 (× 1,000 mmHg/sec) before arrest	9.347 ± 1.713	8.900 ± 1.579	0.205
-dp/dt maximum (× 1,000 mmHg/sec) before arrest	-8.938 ± 1.578	-9.556 ± 2.326	0.193
Cardiac output (mL/min) before arrest	155.55 ± 34.13	149.98 ± 27.27	0.410
VF induction current (mA)	0.59 ± 0.48	0.58 ± 0.69	0.981
CPP before defibrillation (mmHg) during CPR	28.40 ± 10.17	31.01 ± 10.56	0.295
$ETCO_2$ before defibrillation (mmHg) during CPR	13.82 ± 2.17	13.66 ± 2.51	0.912

CPP: coronary perfusion pressure; CPR: cardiopulmonary resuscitation; $ETCO_2$: end-tidal partial pressure of CO_2; VF: ventricular fibrillation.

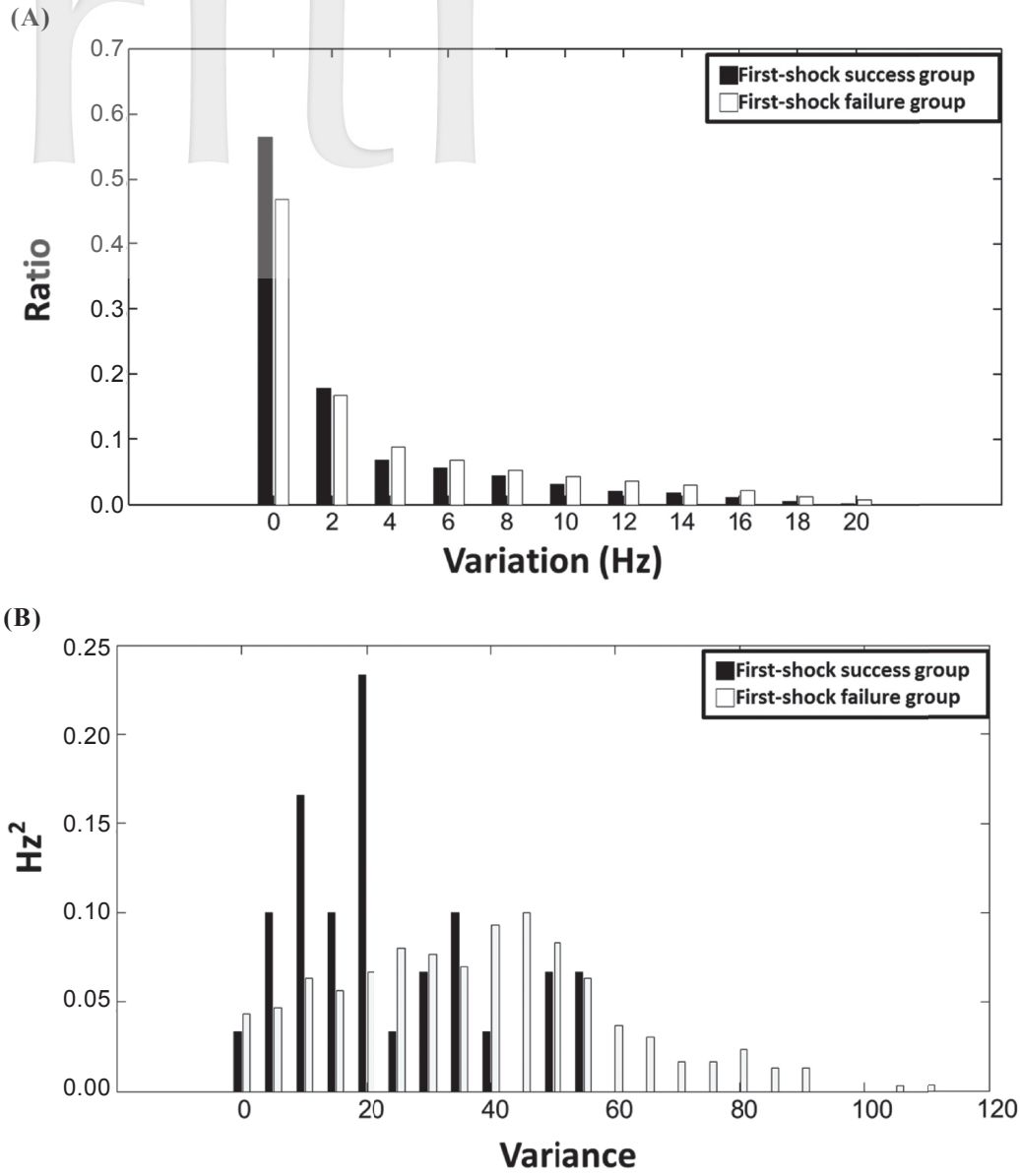

Fig. 2. Distribution of frequency variation and variance of frequency variation between groups. (A) Distribution of frequency variation between the first-shock success group and the first-shock failure group. (B) Distribution of variance of frequency variation between the first-shock success group and the first-shock failure group.

the FVs of an ECG record were outside the range, the successful rate was low. When 88% of the FVs of an ECG record falling in the range from -9.5 to +9.5 Hz was selected as a threshold, the AUC of ROC analysis was 0.708 with sensitivity of 0.800 and specificity of 0.583. Meanwhile, the AMSA analysis of the current study showed the AUC of 0.678 with sensitivity of 0.767 and specificity of 0.547, and the DFA analysis showed the AUC of 0.676 with sensitivity of 0.633 and specificity of 0.690 (Fig. 3 and Table 2). As compared to AMSA and DFA, combining FV and AMSA significantly increases the predictability with AUC of 0.732, sensitivity of 0.933, and specificity of 0.493 (p = 0.005 when compared with AMSA, p = 0.025 when compared with DFA, p = 0.545 when compared with FV).

All the animals in the first-shock success group regained spontaneous circulation, whereas 105 animals in the first-shock failure group did (100.00 vs. 35.00%, $p < 0.001$). In successfully resuscitated animals, the CPR duration of the first-shock success group was significantly shorter than that of the first-shock failure

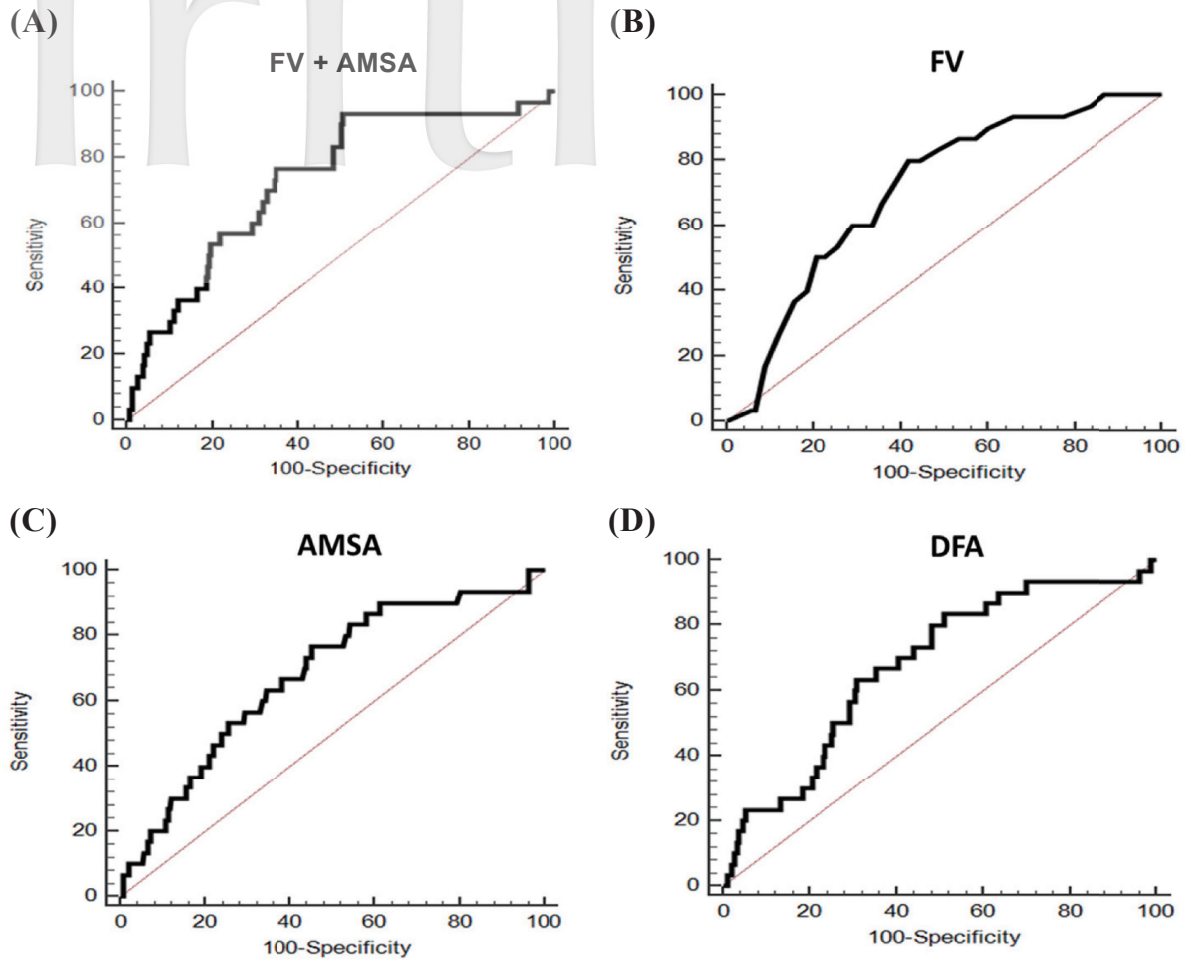

Fig. 3. Receiver operating characteristic (ROC) curves of different waveform analyses. ROC curves of (A) frequency variation (FV) + amplitude spectrum area (AMSA), (B) FV, (C) AMSA, and (D) detrended fluctuation analysis (DFA).

Table 2. Comparison of different methods to predict successful defibrillation

Method	Sensitivity	Specificity	PPV (%)	NPV (%)	AUC	95% CI	*p*
FV + AMSA	0.933	0.493	17.0	98.5	0.732	0.639–0.824	< 0.001
FV	0.800	0.583	17.6	96.3	0.708	0.623–0.792	< 0.001
AMSA[a]	0.767	0.547	15.8	95.5	0.678	0.579–0.777	0.001
DFA[b]	0.633	0.690	18.5	94.4	0.676	0.579–0.774	0.001

AMSA: amplitude spectrum area; AUC: area under curve; CI: confidence interval; DFA: detrended fluctuation analysis; FV: frequency variation; NPV: negative predictive value; PPV: positive predictive value.
[a]$p \leq 0.01$ when compared with FV + AMSA.
[b]$p \leq 0.05$ when compared with FV + AMSA.

group (60.00 ± 0.00 vs. 112.50 ± 26.57 sec, $p < 0.001$). Compared with only one electric shock in the first-shock success group, the resuscitated animals in the first-shock failure group received 2.86 ± 0.80 electric shocks to get ROSC ($p < 0.001$) (Table 3).

Discussion

The use of the frequency variation of VF defined as FV may provide fair predictability for successful defibrillation and modestly improving the sensitivity for predicting the success of defibrillation when

Table 3. Outcomes between groups

Outcome	First-shock success group (n = 30)	First-shock failure group (n = 300)	*p*
ROSC, n (%)	30 (100.00)	105 (35.00)	< 0.001
CPR duration in successfully resuscitated animals (sec)	60.00 ± 0.00	112.50 ± 26.57	< 0.001
Electric shock number in successfully resuscitated animals	1.00 ± 0.00	2.86 ± 0.80	< 0.001

CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation.

combing with the AMSA method. The probability that a defibrillation will result in return of organized rhythm with stationary blood pressure is higher in the animals with small range of FV than that with large one. The AUC of the ROC indicates that the combination of FV and AMSA has a better power to predict whether the defibrillation would be successful or not as compared to FV or AMSA alone.

Animal studies had been performed to describe the organization of myocardial activity during VF.[7,15,20] The phases of VF range from large periodic wavelet transverse the entire heart in the undulatory phase to infrequent episodic electric activity within a limited area of myocardium without conduction to adjacent myocardium in the atonic phase.[15,20] The size of coordinated myocardial fibers decreases as VF persists and the degree of spatial synchrony of epicardium is associated with the possibility of successful restoration of organized electrical activity by electric shock.[21] Presumably, organization of the surface ECG is somewhat related to underlying organization of the myocardial electrical activity. The proposed FV evaluated the FV of VF, which maybe correlated with the organization of VF signals. In the current study, the proposed FV method demonstrates a fair AUC and sensitivity as compared to AMSA and DFA, suggesting that the FV of VF signals may be used to predict the success of defibrillations. The frequency-based nature of the FV method provides a great advantage that the waveform analysis can be performed without interference of ambient electrical noise or artifact from chest compression. Besides, the FV method is not limited by the disadvantage of other frequency-based analyses that sometimes the early and the late VFs both lead to indistinguishable values of frequency.[13,15]

Combination of different methods based on frequency or fractal dimension (amplitude/scaling) may provide more accurate predictability for successful defibrillation than single method. Strohmenger et al. proposed a linear combination of amplitude and frequency (base-line crossings per sec) which more accurately predicted ROSC and hospital discharge in patients with VF cardiac arrest than either measure alone.[22] Another combination of multiple measures including total amplitude, peak-to-peak amplitude, proportion of total power between 2 and 7 Hz, frequency leakage and ScE achieved a greater overall accuracy for predicting ROSC in VF cardiac arrest.[23] By using neural networks, He et al. combined AMSA with previous shock information in OHCA patients which demonstrated an improved performance of defibrillation prediction for subsequent shocks as compared to AMSA alone.[24] In the current study, the FV and AMSA methods usually make different predictions in some ECG data, implying that the FV and the AMSA may capture different characteristics of VF signals that correctly predict the results. Our results demonstrate that the AMSA + FV method can significantly increase the sensitivity while its specificity is maintained a comparable level as compared to the standalone methods.

Limitation

There are several limitations in the current study. To avoid the noise caused by myocardial damage resulted from electric shock, we selected the epoch immediately before first shock only. The criteria of FV in the current study may need to be adjusted when applied to subsequent shocks. Obviously, the results seen in studied animals have not always translated to similar findings in humans. The frequency of fibrillation wavelets in human was lower as compared to the rat model.[22] The applicability of our results may also be limited by the use of young and healthy experimental animals, which were free from underlying heart disease. The waveform characteristics may be

altered in the setting of pre-existing structural heart disease.[25] Besides, time-consumption problem may be proposed when multi-tests were applied. With the help of computer in our following experiment, the real-time analysis was less than 0.1 sec.

Conclusions

The proposed FV method may serve a useful parameter to predict defibrillation success during VF. Combing FV and AMSA increases the prediction performance of defibrillation.

Conflicts of Interest Statement

None.

Acknowledgments

None.

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Supplement Table 1. Variance of frequency variation between groups

Group[a]	Minimum	1st quantile	Median	3rd quantile	Maximum
First-shock success group	0.73	11.99	21.51	36.49	58.09
First-shock failure group	0.00	23.28	39.42	52.88	114.07

[a]$p < 0.001$ between groups.